Yasuda and Mayford (2006) utilized the Morris water maze to track the consolidation-sensitive period and suggested that hippocampus and entorhinal cortex functions as a single unit in regards to the consolidation of spatial memory. However, this argument could be specific to spatial navigation tasks, and there may be temporally and functionally different contributions of medial entorhinal cortex and its upstream regions to other hippocampus-dependent tasks. In fact, a question regarding whether medial temporal lobe structures work in concert to support all forms of declarative memory (Squire et al., 2004) or individual structures are functionally dissociated (Jarrard et al., 2004; Murray et al., 2005) has been debated across species. Further studies are needed to explore possible differential roles of hippocampus and entorhinal cortex in learning and memory.

Overall, it should be appreciated by the community that such a cell-type restricted transgenic mouse strain has been created allowing for temporally discrete genetic control of processes critical to learning and memory. By exchanging the (tet)o mouse of mutant CaMKII gene in the present study with other genes, any genetic manipulation can be targeted to the medial entorhinal cortex and its upstream regions. Genetic dissection of the forebrain in a cell-type-specific manner is challenging because of the lack of appropriate genetic promoters specific to particular areas. However, once created as tetracycline- or Cre recombinase-transgenic mice, they will become valuable research tools for the study of particular brain areas, in particular because cell-type restricted manipulation in vivo is not feasible by conventional lesion techniques with a stereotaxic apparatus.

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# Off on a Tangent: Thalamocortical Axons Traverse a Permissive Corridor across the Basal Telencephalon

**The forebrain is one of most complex cellular structures known. Two phenomena that enable this complexity are tangential migrations that mix neurons from distinct progenitor fields, and axon guidance across intervening, noninnervated fields. A new paper in *Cell* by López-Bendito et al. has discovered the convergence of these phenonema in the critical thalamacortical system.**

With the advent of molecular neuroscience, and particularly of mouse transgenics, there have been major strides in understanding the development of cellular composition and connectivity in the developing forebrain. Prominent among these advances has been the identification of tangential migrations that permit the mixing of neuronal subgroups from distinct progenitor fields, and the molecular regulation of thalamocortical connectivity. Now, a collaborative effort from two labs that have generally focused on either the migration or the connectivity problem has resulted in the remarkable finding that the tangential migration of a defined group of cells, arising from a progenitor field that is distinct from the ultimate destination, is an important step in the guidance of thalamocortical axons toward their cortical targets. In addition to the implications for a critical process in forebrain development, this paper has interesting implications for the processes behind the tremendous expansion of forebrain complexity that has accompanied tetrapod, and especially mammalian, evolution.

The survival of most organisms involves complex interactions between individuals and their environment. As this complexity increases across the animalia kingdom, so does the central nervous system substrate that mediates the animal's processing of sensory information, acting upon this information, and then resensing in the context of expected outcomes. In tetrapod evolution this complexity has been matched by increasing complexity of the forebrain, including the connectivity between thalamic regions that receive most primary sensory input, and more rostral, telencephalic regions that participate in processing this input and formulating

responses. In mammals, expansion of the telencephalic pallium into a layered cerebral cortex, and the extension of thalamostriatal connectivity into this structure, has accompanied the remarkable diversity and flexibility of behavioral repertoires that characterize this class.

With the expansion of the tetrapod forebrain has come an intriguing question: how do thalamic axons negotiate the developmentally and molecularly distinct territories they must cross in order to approach their cortical targets? To accomplish this task they must first migrate ventral-laterally and rostrally from the dorsal thalamus, penetrate the ventral medial telencephalon, then run dorsolaterally through the basal ganglia (Figure 1) (Molnar et al., 2003). Here they initially form a tightly fasciculated band that broadens in the outer striatum as axons target specific cortical regions based on their thalamic origins.

To date, a variety of molecules have been shown to participate in this process, some of which include Slit family proteins that repel thalamic axons from the ventral-medial hypothalamus (Bagri et al., 2002), and Eph/Ephrins that contribute to the specificity of thalamocortical axon innervation within the cortex (Dufour et al., 2003). The April edition of *Cell* includes a paper from López-Bendito et al. (2006) that adds a remarkable twist to thalamocortical axon (TCA) pathfinding. Not only is neuregulin (Nrg1)/ErbB4 signaling added to the list of factors contributing to this process, but TCA guidance through the ventral telencephalon involves a permissive corridor that is formed by the tangential migration of Nrg1-expressing cells from the lateral ganglionic eminence (LGE). Tangential migration is thus shown to not only enhance brain complexity and function by the mixing of neuronal subtypes from distinct subfields of the neuroepithelium, but also to support the guidance of axons whose trajectories have been extended by the evolution of their targets.

The paper begins with the observation that as they course through the mantle region of the medial ganglionic eminence (MGE), TCAs form a corridor between two Nkx2.1 expression domains in the MGE proliferative zone and mantle. Interestingly, many cells within this corridor express markers, including Islet1, Ebf1, and Meis2, suggestive of an origin in the more dorsally located LGE. These cells are present prior to the arrival of the TCAs at E11.5. To show that these "corridor cells" of the MGE mantle indeed migrate tangentially from LGE, migration studies were conducted in telencephalic slice cultures in which migration from homotopic transplants of GFP-expressing tissue was tested. In slices started at E13, a robust migration of Islet1-expressing cells runs ventrally from the LGE, and insertion of a semipermeable membrane between the LGE and the MGE results in a loss of Islet1 expression within the MGE corridor.

This and other evidence supported the novel discovery of a tangential migration of GABA-expressing neurons from the LGE into the MGE mantle that occurs prior to the arrival of the TCAs. To the extent that tangential migration is generally synonymous with non-radial glia guided migration, it should be noted that as analysis of the radial glial scaffold at E14 shows that some radial glial fibers from the LGE course ventrally (for example, see Figure 4 in Misson et al., 1988), it is conceivable that aspects of this migration could be radial glia guided.

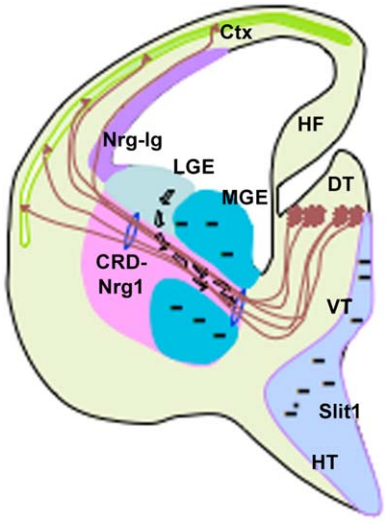


Figure 1. Axon Pathfinding from Dorsal Thalamus to Cerebral Cortex

This schema represents some events affecting axon guidance from dorsal thalamus to the cerebral cortex in mouse, between embryonic days (E) 11.5 and 18. Arrows proceeding from the lateral ganglionic eminence (LGE) represent the tangential migration of cells that will form a permissive corridor for the passage of thalamocortical axons through the relatively nonpermissive medial ganglionic eminence (MGE; light blue). In addition to the permissive substrate provided by the CRD-Nrg1 domain (pink), this general region expresses other factors, including semaphorins and netrin-1 that appear to influence fasciculation and outgrowth of TCAs (Braisted et al., 2000; Wiencken-Barger et al., 2004). DT, dorsal thalamus; VT, ventral thalamus; HT, hypothalamus; HF, hippocampal formation; CTX, cortex.

Next, the authors use an elegant series of slice transplants to show that the LGE-derived corridor cells form a permissive substrate for TCAs that is important for their progression through the MGE mantle. Key to these experiments is the finding that pieces of dorsal thalamus, placed in the ventral telencephalon close to the position where the TCAs would normally penetrate this structure, grow robustly and preferentially into the MGE corridor and dorsolaterally toward the overlying cortex. Heterotopic transplants revealed that TCAs strongly prefer the corridor cells to Nkx2.1-expressing MGE tissue. Mash1 mutants, in which corridor cells fail to form and TCAs fail to progress normally through the ventral telencephalon, were then used in an impressive series of rescue experiments. Homotopic LGE transplants placed on *Mash1*$^{-/-}$ slices give rise to a ventral migration of corridor cells that rescue the dorsolateral progression of *Mash1*$^{-/-}$ TCAs.

Having demonstrated that the corridor cells provide the TCAs with a permissive strip through the relatively nonpermissive MGE, the authors focused on the molecular cues that mediate this signal. The membrane-bound form of neuregulin, CRD-NRG1, is strongly expressed in the MGE corridor (Flames et al., 2004). To determine whether CRD-NRG1 expression mediates the permissive nature of the corridor cells for TCA axons, COS cells overexpressing CRD-NRG1 promote the directional growth of TCAs. In addition, CRD-NRG1 mutant mice show abnormal TCA axon outgrowth in the MGE.

The continuation of many TCAs through the ventral telencephalon of CRD-NRG1 nulls prompted the search for other molecules that might attract TCAs to the

cortex. In a previous paper from the Marin and Rubenstein labs, mRNA for the diffusible form of Nrg1, Ig-Nrg1, was found to be expressed in the cortical proliferative zone, with the strongest region of expression in the striatopallial angle. This expression provides a chemoattractant signal for interneurons migrating dorsally from the ganglionic eminences (Flames et al., 2004). To determine whether Ig-NRG1 also promotes TCA growth into the cortex, the authors first cultured E13.5 thalamic explants in three-dimensional matrices with Ig-NRG1-expressing COS cells. This treatment resulted in a large, nondirectional outgrowth of processes from the explants. Here it would be interesting to know whether limiting dilutions of Ig-NRG1, presented to the axon growth cones in a system where these are isolated from the cell somas, could in fact promote a chemoattractant response.

Follow-up experiments showed that ablation of the Ig-Nrg1 expression domain in the striatopallial angle results in limited TCA axon progression toward the dorsal cortex. Critically, this effect was rescued by replacement of the ablated tissue with Ig-NRG1-expressing COS cells. Finally, telencephalic-specific knockouts of Nrg-1 have greatly reduced progression of TCA axons through the ventral telencephalon, although this effect lessens by birth. This effect is largely phenocopied in mice lacking ErbB4, a receptor for Nrg-1 that appears to be expressed in TCAs. The authors complete their extraordinary depth of experimentation by demonstrating that the ErbB4 KO effect on TCA progression in the ventral telencephalon is almost certainly cell-autonomous.

Taken together, the results summarized above represent a major advance in understanding TCA guidance through the ventral telencephalon. Beginning at E11.5, a tangential migration of neurons from the LGE brings CRD-NRG1-expressing cells into position within a strip of MGE that lies between strongly Nkx2.1-expressing regions of the MGE proliferative zone and MGE mantle. Next, TCAs expressing the ErbB4 receptor penetrate the ventral telencephalon and progress preferentially on the CRD-NRG1 corridor. Expression of a diffusible form of NRG1 in the ventral and lateral pallium then stimulates the growth of these axons through the dorsal striatum and into the cortex.

These results have important implications for the interpretation of previous studies on TCA pathfinding, for consideration of the role of tangential migration in promoting evolution of axon pathfinding, and for directing progress in understanding neuropsychiatric conditions that may include TCA abnormalities. First, it has been suggested that TCAs may initially be guided by pioneer axons projecting from the ventral telencephalon back into the thalamus (Metin and Godement, 1996), and then by corticofugal axons that guide the TCAs from the internal capsule into the cerebral cortex (Molnar and Blakemore, 1995). The present study by no means disproves a role for axo-axonic interactions in TCA pathfinding, but the interpretation of data previously thought to be supportive of this mechanism needs to be revisited. For example, abnormal progression of TCAs have been noted in several mouse mutants, involving cortically expressed genes, in which a contributory defect could be attributed to the lack of corticofugal axon progression through the internal capsule (Hevner et al., 2002; Molnar et al., 2003). Based on the current study, an additional possibility could relate to a loss of Nrg1 in the cortex of these mutants. In the case of mutants for Pax6, in which the gene is strongly expressed in the cortex and weakly expressed in the LGE, migration or specification of corridor cells could even be affected.

Second, this paper suggests a novel mechanism affecting the evolution of the forebrain. In the forebrain, axons often traverse molecularly distinct regions to reach their ultimate targets. In the case of TCAs, these regions include the ventral thalamus and the MGE and LGE of the ventral telencephalon. Common sense, albeit a dangerous source of reasoning when applied to evolution, suggests that TCAs would benefit from the presence of a permissive corridor through the tissue that does not attract its innervation to reach the tissue that does. So why is the corridor formed by tangential migration of LGE cells rather than radial migration from the MGE? The reason could lie in the fact that, in relative contrast to the globus pallidus region that is a presumptive mantle region of the MGE, dorsal thalamic axons do innervate the striatal mantle that derives from the LGE. During tetrapod evolution, thalamostriatal innervation has become less robust, particularly in mammals, where the cerebral cortex has become the primary location of higher-order sensory processing (Marin et al., 1998). Thus, a non-radial glia guided migration allows cells from the evolutionarily previous main target of those axons to form a permissive corridor for their extension into the overlying cortex. As a large Nkx2.1-expressing, MGE-like region also exists in amphibians (Gonzalez et al., 2002), it would be interesting to know whether a similar tangential migration from more dorsal regions of the subpallial telencephalon also exists in this class of animals.

Third, the results of this paper could have important clinical implications. Although no specific diseases of TCAs are known, a deficit in thalamocortical connectivity has been postulated to contribute to symptoms of both autism and schizophrenia. In the case of schizophrenia, in dorsomedial prefrontal cortex there is a large reduction of dendritic spines on the basilar dendrites of layer 3 pyramidal neurons that is consistent with a deficit of TCAs (Glantz and Lewis, 2001). The specificity of this effect across cortical regions is unclear, but an alteration of Ig-NRG1/ErbB4 signaling could be hypothesized to particularly effect medial cortical regions. In fact, linkage of polymorphisms within both the Nrg1 and ErbB4 genes has been reported and (sometimes) replicated in familial schizophrenia (Harrison and Law, 2006; Silberberg et al., 2006). The study of López-Bendito, Cautinat, and others thus provides strong rationale for closer evaluation of thalamocortical connectivity in schizophrenia, perhaps by combining genetics and brain imaging.

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# Envisioning the Reward

**The primary visual cortex (area V1) is for vision. At least, that is what most researchers believe. However, in a recent issue of *Science*, Shuler and Bear demonstrate a correlate of reward timing in area V1. This surprising result indicates that brain circuits for reward processing are more extensive than expected and that area V1 has more functionality than previously thought.**

How do animals learn to associate an appropriate behavioral response with a particular stimulus? They can learn by trying out various responses and by monitoring the ensuing rewards and punishments (e.g., Pearce and Hall, 1980). All that is needed in this form of learning (instrumental conditioning) is that correct responses are followed by a reward, while incorrect responses are not. Animals are also capable of learning the correct response when rewards are delivered after a delay. In this case, the animal should learn not only the association between the stimulus, the response, and the reward, but also when to expect the reward (Sutton and Barto, 1998; Schultz and Dickinson, 2000).

Neuronal activity related to reward delivery and reward timing has been observed in several brain regions, including the substantia nigra and the ventral tegmental area (Schultz and Dickinson, 2000), striatum (Morris et al., 2004), amygdala (Paton et al., 2006), parietal cortex (Glimcher, 2004), and frontal cortex (Tremblay and Schultz, 2000). Reward coding has so far not been observed in early sensory areas like the primary visual cortex (e.g., in monkeys; P.R.R., unpublished data). This situation has now been changed by a recent report by Shuler and Bear (2006) in *Science*, who demonstrate that activity related to reward delivery and reward timing can occur at the earliest stages of visual information processing. They found that, when adult rats experienced a pairing between a visual stimulus and a subsequent reward, a substantial fraction of neurons in the primary visual cortex began to express activity that predicted the timing of the reward.

In Shuler and Bear's experiment, rats had to lick a water tube in response to a visual stimulus to obtain a reward in the form of a drop of water (Figure 1A). The visual stimulus was presented via head-mounted goggles, which delivered large-field retinal illumination for 0.4 s to either the right or the left eye whenever the rats came near a water tube. The drop of water was given after a delay that was different for right and left eye stimulation. After stimulation of the left eye, the rat had to lick the water tube a few times (six or ten licks) to receive the reward, whereas after stimulation of the right eye it had to lick twice as many times. During the task, the activity of neurons in the primary visual cortex was monitored with chronically implanted arrays of microelectrodes.

In animals inexperienced with the task, V1 responses were found to be directly related to the physical aspects of the stimulus, such as onset, offset, and duration of the retinal illumination. Thus, in this phase, the neurons behaved just like ordinary neurons in an early visual area. However, once the animals had become proficient in the task (after three to seven training sessions), a significant proportion of neurons began to show activity that correlated with the time that the reward was given. Figure 1C shows a neuron with a poststimulus response that peaks at reward time. The response was not a result of the delivery of reward itself, because on unrewarded trials (Figure 1C, top right) the neuron showed the same response as on rewarded trials. Other neurons were found that signaled reward time by a sustained increase or a sustained decrease in their response until the reward was expected.

Another remarkable finding was that poststimulus activity related to reward timing was triggered in any given neuron by stimulation of either the left or the right eye (but not both). For the neuron shown in Figure 1C, for example, reward timing activity only occurred in response to stimulation of the left eye, and not in response to stimulation of the right eye (Figure 1C, bottom two panels). This excludes the possibility that the neuronal activity is a direct reflection of the animal's arousal, which would be similar for left and right eye stimulation. Moreover, the reward timing activity continued to be evoked by the same visual stimuli when the animals were not performing the task—that is, in sessions where access to the water tube was obstructed.

How are neurons in the primary visual cortex informed about the timing of rewards? Shuler and Bear do not speculate on this, but one possibility would be through feedback connections. Not only does the primary visual cortex project to higher cortical areas, but it also receives extensive feedback connections from these